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TITLE: Early Post Traumatic Seizures in Military Personnel Result in Long Term Disability

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ABSTRACT:

This study is predicated on substantial evidence that early post-traumatic seizures occur frequently and create a metabolic crisis that will lead to cell death of hippocampal tissue among persons who have sustained a traumatic brain injury (TBI). Our central hypothesis is that early post-traumatic seizures are acutely injurious due to increases in intracranial pressure and acute edema of the hippocampus leading to delayed long term hippocampal atrophy. This represents a unique translational hypothesis that we are uniquely qualified to study. In this study we plan to perform continuous EEG monitoring of military and civilian TBI patients for the initial 7 days after TBI to assess for non-convulsive seizures. This is followed by evaluating these same subjects at 6 months after injury by volumetric MRI of the hippocampus and cognitive testing to assess for disturbances of memory-related cognition and post-traumatic stress. We have begun to study civilian TBI patients in year 1 and have worked on establishing methodology and connectivity and IRB permission at military sites in year 1.

Subject Terms: Traumatic brain injury, blast injury, seizures, brain atrophy

INTRODUCTION:

Over 20% of brain injured patients have seizures within 1 week after injury when monitored intensively by continuous electroencephalography (cEEG). With the use of continuous EEG monitoring, we have demonstrated that the incidence of electrographic seizures and clinical seizures is higher, in the range of 20-25%. In the study by Vespa et al, seizures occurred within the initial week after injury and were not associated with the specific type of injury (i.e. contusional versus non-contusional). The seizures occurred repeatedly in nearly ¼ of patients are 1/3 of those with seizures had status epilepticus. In over ½ of the patients, the seizures were nonconvulsive in nature and could not be detected without EEG monitoring. Post-traumatic seizures have been associated with neurochemical signs of cellular distress, secondary excitotoxicity, secondary cellular membrane damage and prolonged elevations of intracranial pressure. Seizures can be readily identified and treated during the critical phases of injury, if the appropriate personnel and monitoring are available. In this study we plan to perform continuous EEG monitoring of military and civilian TBI patients for the initial 7 days after TBI to assess for non-convulsive seizures. This is followed by evaluating these same subjects at 6 months after injury by volumetric MRI of the hippocampus and cognitive testing to assess for disturbances of memory-related cognition and post-traumatic stress.

BODY: Three technical progress reports have been submitted prior to this date.

The following institutions will be involved:
- University of California Los Angeles Medical Center
- Walter Reed Army Medical Center
- National Naval Medical Center

Investigators are:

- Paul Vespa, MD, (UCLA neurointensivist) (Principal Investigator)
- LCDR Etienne Mill (Neurologist at NNMC Bethesda)
- Col. Rocco Armonda, MD (Lead Neurosurgeon for TBI at USNMC Bethesda)
- CDR. Lisa Mulligan, MD (Integrated Service Chief of Neurosurgery NNMC)

Research accomplishments by specific aims:

Specific Aim 1: To determine the incidence of post-traumatic seizures in military TBI victims who have undergone continuous EEG (cEEG) monitoring as standard of care.

Accomplishments: We have begun collecting data on civilians. We are working on the infrastructure necessary to collect information on military TBI.

Specific Aim 2: To determine if early post-traumatic seizures on cEEG result in long-term atrophy of the brain hippocampus on MRI scans at 6 months.

Accomplishments: We have studied the effects of seizures in civilians and report a positive relationship (see the appended article in press).

Specific Aim 3: To determine if the occurrence of post-traumatic seizures results in worsened memory-related cognitive outcome and PTSD as compared with those without seizures.

Accomplishments: This aim has not yet started.

The timeline and milestones for the work over the 4-year performance period are as follows:

1. Study initiation, regulatory review and approval: Yr 01 Mo 1-6;. **PROGRESS: UCLA has local and HRPO IRB approval. NNMC and WRAIR IRB process is underway. This is the result of ongoing weekly work by the study staff at UCLA and DOD.**
2. Study hardware and software roll-outs, connections and testing: Yr 01 Mo 1-6; **PROGRESS: 1) Creation of secure network for data transfer between NNMC and UCLA. 2) IRB submission and multiple revisions submissions by Dr. Mill Etienne. 3) Ongoing civilian enrollment at UCLA with data capture for EEG and MRI imaging. 4) Data analysis for EEG and MRI in the civilian cohort.**

3. Deliverable #1: Report of regulatory approvals and system-wide readiness for study initiation: Yr 01 Mo 6; **PROGRESS: UCLA has local and HRPO IRB approval. NNMC process is underway. Dr. Mill Etienne has the primary responsibilities for this at NNMC.**

4. Screening, recruitment, and enrollment of study participants, plus interim analysis as warranted by study accrual: Yr 01 Mo 6 - Yr 03 Mo 5; **PROGRESS: No progress on this yet at the NNMC, but we continue to make good progress at the UCLA site. We have enrolled 25 subjects since March 1, 2009.**

5. Deliverables #2 - #7: Report of screening, recruitment and enrollment of participants and interim analyses: Yr 01 Mo 12, Yr 02 Mo 6 and 12, Yr 03 Mo 6 and 12, Yr 04 Mo 5; **PROGRESS: We continue to screen at UCLA but have not begun at NNMC.**

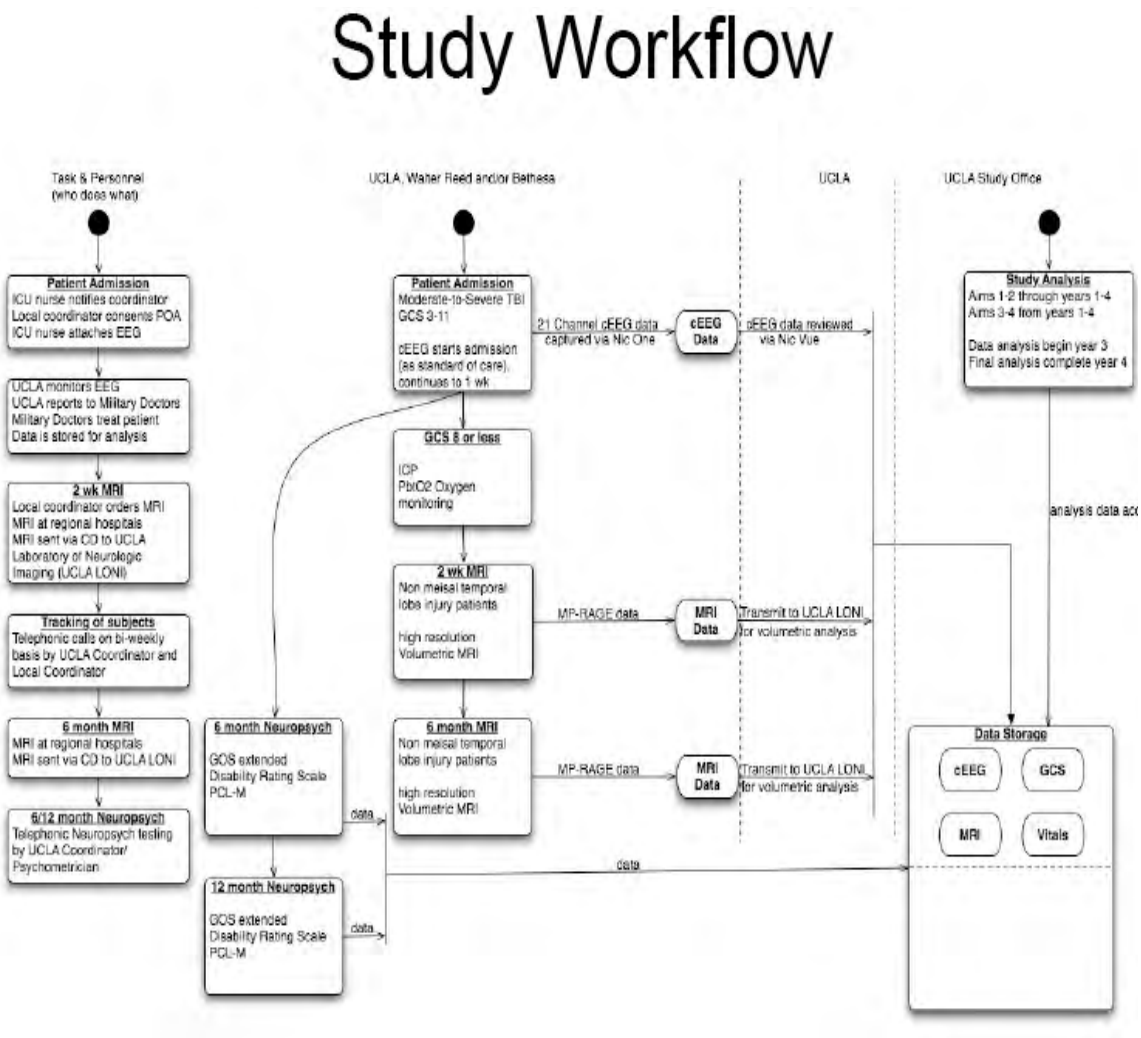
6. Concluding analyses, professional presentations and publications: Yr 04 Mo 6-12; **PROGRESS: 1) We presented our preliminary findings at the 2009 Military Health Research Forum in Kansas City during the dates of August 30-Septembe 3, 2009. We presented a poster and discussion of the study design and the preliminary data from the UCLA Civilian Cohort. 2) Dr. Vespa presented the program to Major General Rubinstein during a site visit by the General to UCLA. Indepth discussion about the potential applications of this model were outlined. 3) Dr. Vespa presented the ongoing work to the Secretary of the Navy Ray Mabus on October 22, 2009 udinr the UCLA Operation Mend Site Visit. The Secretary was impressed and pledged to create enhanced clinical applications of this work. 4) Dr. Vespa presented the research plan for Admiral Mike Mullen on November 12, 2010. 5) Dr. Vespa is scheduled to present this project and a proposed down-range cEEG monitoring project in Afghanistan and other eschelons of care to the Blue Ribbon Symposium on TBI and PTSD that is being convened by the Assistant Commandant of the Marine Corps (ACMC) and the Army Vice Chief of Staff (VCSA) on December 16-17, 2010 at the National Intrepid Center of Excellence in Bethesda.**

-7. Final deliverable: Report of study findings, presentations, publications, and recommendations: Yr 04 Mo 12. **PROGRESS: Not applicable yet.**

Preliminary Data:

We enclose the recently published manuscript to the journal Neurology. This article is appended to this report and outlines our preliminary experience with the civilian TBI population. We have not yet started to collect data from military TBI population.

Preliminary progress on establishing a study work flow has been made. A synopsis of this work flow is outlined below.



Preliminary progress on establishing the technical infrastructure at the NNMA has been made. However, we have been unable to start cEEG monitoring on military TBI patients and have been unable to start enrollment of military subjects. Detailed telephone and email discussions between our team and NNMC IT staff, including completing a 45 item technical requirements questionnaire have been done. These results are summarized as follows:

1. The B2B gateway requirements template was established by NNMC.

2. Purchase of Juniper SSG20

4. Specified the required ports for firewall access, to pass data to UCLA.

The IT limitations at NNMC are impeding the progress of this study at NNMC. We are endeavoring to negotiate this difficult pathway with NNMC.

NARRATIVE OF PROGRESS AND PROBLEMS

The ongoing work for this project has consisted of weekly teleconferences for planning to get the EEG system at Bethsda NNMC upgraded to be on par with UCLA for the purposes of performing this project. These conferences include key personnel from NNMC, mostly Dr. Mil and the IT staff at NNMC. Several important roadblocks have been identified:

1) EEG Upgrade at Bethesda NNMC. Dr. Mil requested some assistance from his department chair, and after a few weeks, the department chair pledged to pay for the EEG upgrade. The upgrade has been blocked by NNMC due to local reasons not easily explanable to me.
2) IRB approval at Betheda: We have been unable enroll subjects for any component of this research at NNMC due to lack of IRB approval. Ms. Mill Etienne has been processing the IRB submission, but the IRB submission has been delayed by the delays in IT approval.
3) IT issues at NNMC: Basim Faris, our IT engineer for UCLA, has attempted to engage the IT personnel at NNMC. A detailed questionnaire about the types of connections and data transfer was completed by Basim Faris. However, more questions and clarifications were called for by NNMC IT. Specific software B to B gateway was approved by NNMC IT and accepted by UCLA. This is now ready to use.
4) Enrollment of subjects at UCLA has continued with good progress. We have enrolled 10 patients at UCLA in 2011. We continue to study all aspects of the specific aims for these subjects.

KEY RESEARCH ACCOMPLISHMENTS:

1. Publication of the preliminary data in civilian TBI in Neurology 2010 (in press). “Nonconvulsive Seizures after Traumatic Brain Injury are Associated with Hippocampal Atrophy”. Neurology
2. IRB approval at UCLA and Military Central IRB.

REPORTABLE OUTCOMES:

Publication of the preliminary data in civilian TBI in Neurology 2010 (in press). “Nonconvulsive Seizures after Traumatic Brain Injury are Associated with Hippocampal Atrophy”. **Neurology. 2010 Aug 31;75(9):792-8. PMID: 20805525.**

CONCLUSION:

We have begun our research in civilian TBI with very promising results that suggest an association between early post-traumatic seizures and delayed hippocampal atrophy. We continue to work on establishing the proper infrastructure at NNMC to start studying

military TBI.

REFERENCES: none

APPENDICES:

1. Journal article in press: “Nonconvulsive Seizures after Traumatic Brain Injury are Associated with Hippocampal Atrophy”. **Neurology. 2010 Aug 31;75(9):792-8. PMID: 20805525.**